

Remarks

35 USC §112

Claims 11-23, 25, 27-28 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner states that claims 11-29 recites the dependency from deleted claims.

Applicants corrected these dependencies in Applicant's response to the Restriction Requirement dated May 9, 2006. A copy of the amended claims submitted in Applicant's response to the Restriction Requirement is included in this response under "Amendments to the Claims".

Accordingly, Applicants respectfully request that the 35 U.S.C. §112, second paragraph rejection of claims 11-23, 25 and 27-28 be withdrawn.

35 USC §102

Claims 10-19, 21, 27-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Gerspacher et al. (WO 98/07694). Applicants respectfully traverse.

Gerspacher (WO 98/07694 Novartis Case 21011) discloses that acylaminoalkenylene-amide derivatives of formula I are useful as NK1 and NK2 antagonists for treating diseases of the gastrointestinal tract, such as Crohn's disease, Hirschsprung's disease, diarrhea, mal-absorption conditions, inflammatory conditions" and "ulcerative colitis". However the present invention, however, is directed to a method of treating a separate class of diseases, namely **functional motility disorders of the viscera**.

Functional motility disorders of the viscera are defined in the first paragraph of page 2 of the specification as including those associated with visceral hypersensitivity and/or altered motor responses. Enclosed is a review article by H Mertz from *Alimentary Pharmacology & Therapeutics* (2003) that discusses the importance of visceral hypersensitivity in understanding and finding new treatments for functional gastrointestinal disorders.

A functional disorder is a disorder or disease where the primary abnormality is an altered physiological function rather than an identifiable structural or biochemical cause. In general such disorders cannot be diagnosed in a traditional way i.e. they cannot be diagnosed by

examination, x-ray, or laboratory tests that are commonly used to diagnose structural abnormalities or inflammatory or infectious diseases.

Crohn's disease is a disease of the gastrointestinal tract but it is not a functional motility disorder of the viscera. It is a non-specific chronic transmural inflammatory disease that most commonly affects the distal ileum and colon but may occur in any part of the gastrointestinal tract.

Hirschsprung's disease is a disease of the gastrointestinal tract but it is not a functional motility disorder of the viscera. It is caused by the congenital absence of Meissner's and Auerbach's autonomic plexus in the bowel wall, usually limited to the distal colon. Hence, distal colonic peristalsis is absent or abnormal, resulting in continuous smooth muscle spasm and partial or complete obstruction with accumulation of bowel contents and massive dilation of the more proximal, normally innervated bowel.

Diarrhea is not a functional motility disorder of the viscera either. It has various infectious, inflammatory, drug-induced, food-related, post-surgical, transit-related and psychological causes. These may produce diarrhea by four distinct mechanisms: inflammation, increased osmotic load, increased secretion, and decreased absorption time. Hence, diarrhea is a **symptom** of a number of disorders. It is not a disease as such.

Gerspacher (WO 98/07694 Novartis Case 21011) does not disclose a method of the treating functional motility disorders of the viscera using compounds of formula I so the invention as claimed in claims 10-19,21,27-29 is novel.

Based on the foregoing, Applicants respectfully request that the 35 U.S.C. §102(b) rejection of claims 10-19, 21 and 27-29 be reconsidered and withdrawn.

35 USC §103

The Examiner has rejected claims 22-26 under 35 U.S.C. 103(a) as being obvious over Gerspacher et al. (WO 98/07694) in view of Ksander et al. (US 5217996). Applicants respectfully traverse.

Gerspacher discloses acylaminoalkenylene-amide derivatives of formula I and IA of the claimed invention that are NK1 and NK2 antagonists. The Examiner acknowledges Gerspacher does not disclose the use of such compounds for the treatment of diarrhea-predominant irritable

bowel syndrome. Gerspacher does not disclose the use of such compounds for the treatment of irritable bowel syndrome generally either.

Ksander discloses biaryl substituted 4-amino-butyric acid amides and their use as neutral endopeptidase (NEP) inhibitors in the treatment of conditions and disorders responsive to inhibition of NEP, particularly cardiovascular disorders, such as hypertension, renal insufficiency including edema and salt retention, pulmonary edema and congestive heart failure (see column 2, paragraph 2). Ksander suggests the compounds **may** also be useful for treating pain, depression and certain psychotic conditions. Ksander also lists various **potential** indications including gastrointestinal disorders such as diarrhea and irritable bowel syndrome (column 1, lines 35-37).

Ksander does not disclose any acylaminoalkenylene-amide derivatives of formula I (or IA) of the claimed invention. The similarity in structures of formula I of the claimed invention and formula I of Ksander is merely superficial. They are in fact chemically distinct in terms of structure as well as activity.

Although Ksander mentions irritable bowel syndrome and diarrhea as potential indications in the summary of invention this appears to be purely speculative. No support is given for this assertion other than biaryl substituted 4-amino-butyric acid amides are apparently NEP inhibitors.

There is therefore no reason for one of ordinary skill in the art before the priority date to combine the teachings of Gerspacher and Ksander without knowledge of the claimed invention.

And in any event, given the differences in chemical structure and activity one could not have predicted that the compounds of the present invention would be effective in treating irritable bowel syndrome.

The invention as claimed in claims 22-26 is therefore not obvious over Gerspacher in view of Ksander.


Based on the foregoing, Applicants respectfully request that the 35 U.S.C. §103(a) rejection of claims 22-26 be reconsidered and withdrawn.

In view of the remarks and amendments, further and favorable consideration of the present application and the allowance of all pending claims are respectfully requested. The

In view of the remarks and amendments, further and favorable consideration of the present application and the allowance of all pending claims are respectfully requested. The Examiner is also invited to contact the undersigned should the Examiner believe that such contact would expedite prosecution of the present application.

Respectfully submitted,

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